REMARKS

In response to the Final Office Action mailed January 3, 2007, Claims 1 and 3-15 stand pending. Claims 3, 7 and 9-11 stand withdrawn pursuant to restriction requirement. Claims 1, 4-6, 8 and 12-15 stand rejected. Claim 4 has been cancelled. Claims 1, 13 and 14 have been amended. No new matter has been added by virtue of these amendments.

Claim Rejections

1. Claims 1, 4-6, 8 and 12-13 stand rejected under § 103(a) as being unpatentable over Date et al (Oncogene, 17:3045-3054, 1998) in view of Bartley (US Pat. No. 5,766,581). Applicants respectfully traverse this rejection.

Date et al is asserted to merely disclose that HGF contains a four-kringle-containing (NK4) growth factor of 59 kDa protein. The Examiner has previously acknowledged that Date does not teach attaching a polyethylene glycol group (PEG) having a molecular weight of about 20-40 kDa that forms an amide bond with the NK4 polypeptide.

Bartley et al is asserted to teach pegylation of a MGDF protein via branched or unbranched PEG (including monoethoxy polyethylene glycol) in the range of only 12-25 kDa to the N terminus of the lysine residue or via an amide bond at the N-terminus of the protein. Bartley is also asserted to teach pharmaceutical compositions of said peg-modified protein. Applicants respectfully traverse and overcome this rejection.

However, Bartley only discloses peg-modification of MGDFs (MP11.z and s) or megakaryocte growth and development factors and related proteins. There is no correlation or apparent teaching of peg-modified MGDFs with any other unrelated protein, much less HGF or NK4. Contrary to the Examiner's assertion that it would be

obvious to try the method of Bartley to the HGF of Date, there is no teaching in Bartley that its method would work on any other protein which is unrelated to MGDF protein.

In column 5, lines 21 to 23, Bartley et al. expressly admits that "should be noted that the effect of modification of a particular protein cannot be predicted". (emphasis added) Thus, Bartley et al at best only teach how to modify MGDF protein but do not teach how to modify HGF or NK4, respectively. Bartley again admits this unpredictability in column 6, lines 15 to 20, "the ability to modify MGDF is unknown in the art since the susceptibility of each individual protein to modification is determined by the specific structural parameters of that protein. Moreover, the effect of such a modification on the biological properties of each protein is unpredictable from the art" (emphasis added), and further in lines 43 to 46 of the same column "for example, it has been shown that in the case of nonselective conjugation of superoxide dismutase with polyethylene glycol, several fractions of the modified enzyme were completely inactive (P. McGoff et al.)". Bartley et al. were themselves not even sure about the outcome of their own experiments as shown in column 23, lines 57 to 60, admitting that "however, the polymer/MGDF molecule disclosed herein may have additional activities, enhanced or reduced activities, or other characteristics, as compared to the non-derivatized molecule" (emphasis added).

Applicants' invention is directed to the attachment of one PEG-moiety with a molecular weight of 30 to 40 kDa to HGF/NK4 via an amide bond. Bartley et al only discloses the attachment of PEG to MGDF and expressly admits and recognizes the unpredictability of modifying any protein. This recognized unpredictability in the art is also disclosed by Applicants' specification, wherein the Mehvar (2000) reference (which was published two years after Bartley) states that conjugation of different polyethylene glycols to Il-8 and G-CSF as well as other interleukins results in the production of molecules with impaired properties (spec at para 5). Furthermore, Francis et al (1998) posits that "pegylation of proteins is always based on trial and error and virtually all parameters of such a pegylation can have a surprising and very profound effect on the

functionality of the product" (spec at para 6). Finally, as disclosed in our specification, Reddy (2000) states that each protein requires different optimization chemistry and therefore the influence of pegylation cannot be predicted.

The cited references of Date and Bartley (and the Examiner's cited quotations of Reddy, Mehvar and Francis) must be read in their entirety. Applicants respectfully submit that, the teachings of these references, read in their entirety, demonstrate and disclose that "modification on the biological properties of each protein is unpredictable from the art" (Bartley, emphasis added) and that pegylated modifications to other proteins unrelated to MGDF have resulted in production of molecules with impaired properties (Mehvar). Applicants respectfully posit that, contrary to the Examiner's "cherry-picking" of some comments, that the references in their entirety teach the unpredictable nature of pegylating different type proteins.

Moreover, the cited references in combination do not teach nor disclose each and every element of Applicant's Claim 1. Neither Date nor Bartley teach how to optimize HGF or NK4. Bartley does not further even teach how to peg modify any protein, including even MGDF, above 25 kDa. Therefore, the combination of Date and Bartley, even presuming arguendo the presence of a motivation to combine said references, would not meet each and every element/limitation of Claim 1 as currently amended. Respectfully, Claim 1 thus is not anticipated by the combination of Date and Bartley.

Accordingly, Applicants respectfully submit that the cited references do not teach or render obvious Applicants' invention, but rather teach away from same. Furthermore, the cited references do not, either singularly or in combination, meet each and every element of Applicant's invention. Applicants therefore respectfully request that claims 1, 5-6, 8 and 12-13, as amended, are thus in condition for allowance.

2. Claims 14 and 15 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Date et al and Bartley et al as applied to claims 1, 4-6, 8, and 12-13 above, and further in view of Veronese et al. (US Pat. No. 6,528,485 B1). While the Examiner has acknowledged that Date in combination of Bartley do not teach a pharmaceutical of a monoPEGylated conjugate comprising at least 90% or 92% of the total NK4 molecule, the Examiner asserts that Veronese et al teaches making PEGylated proteins and purifying them to greater than 92% purity and also would teach that a high purity PEGylated protein results in a better bioavailability and pharmacokinetics profile in vivo. Applicants respectfully traverse and overcome this rejection.

However, the addition of the Veronese reference to the above-described references does not overcome the deficiencies of said references and thus does not render Applicants' invention obvious. Veronese concerns the pegylation of HGRF only. It does not address pegylation at any other protein (much less pegylation of NK4) and requires unique coupling conditions optimized for hGRF wherein, in contrast to the current invention, the PEG is coupled to the protein via a norleucine or lysine linker and not via a monomethoxy linker. In fact, Veronese only claims a peg-hgf complex that does not contain a triazine group. Indeed, there is no showing that the unique coupling conditions required for the Veronese method of pegylation of HGRF would even work with the Bartley method or vice-versa. Accordingly, the Veronese method of pegylation conflicts with Bartley's methodn and thus there would be no motivation to combine the two references.

Moreover, and in support of Applicants' invention, Veronese specifically admits that "site-specific pegylation remains a chemical challenge." Therefore, there would be and is no motivation to combine Veronese with Bartley, as both Veronese and Bartley recognize the unpredictability of pegylation and each use different methods to achieve and couple said pegylation with different proteins. The combination of references therefore would not meet each and every element of Applicant's claim 1.

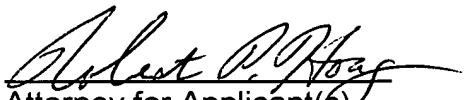
Finally, the combination of Veronese does not address the failure of the Date and Bartley references to teach pegylation of NK4 with a 30kDa to 40kDa pegylated group. Veronese does not teach NK4, nor how to pegylate said molecule, nor the size of said pegylated group. Date does not teach how to pegylate said NK4, nor the size of any pegylated group. Bartley does not teach how to pegylate said NK4, nor the size of a 30kDa to 40kDa pegylated group. Since neither reference, singularly or in combination, teach each and every element of Applicant's claim 1, Applicants respectfully submit that said combination of references do not render Applicant's Claim 1, 5-6, 8 and 13-15 obvious.

Since Veronese does not supply any motivation to combine the prior references, nor provide any details for preparing the PEGylated compounds of the present claimed invention but instead admits the specific challenges associated with PEGylation (and in fact teaches away from the method of Bartley in said pegylation), Applicants respectfully suggest that claims 14 and 15 are thus not obvious for the reasons stated above.

As the cited references do not teach Applicant's invention, but instead actually teach away from Applicants' invention, Applicants respectfully submit that such references can not be properly combined. Applicants respectfully submit that accordingly claims 14-15 are now in condition for allowance.

No further fee is required in connection the filing of this Amendment. If any additional fees are deemed necessary, authorization is given to charge the amount of any such fee to Deposit Account No. 08-2525.

Respectfully submitted,



Attorney for Applicant(s)
Robert P. Hoag
(Reg. No. 39712)
340 Kingsland Street
Nutley, NJ 07110
Telephone (973) 235-4453
Telefax: (973) 235-2363

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